SECTION 4. PLANNING THE 2000 FSIS DOMESTIC MONITORING PLAN AND SPECIAL PROJECTS: VETERINARY DRUGS

PHASE I - GENERATING AND RANKING LIST OF CANDIDATE COMPOUNDS

LIST OF CANDIDATE COMPOUNDS

The candidate veterinary drugs of concern selected by members of the Surveillance Advisory Team (SAT) are presented below. Since the Food Safety and Inspection Service (FSIS) wishes to prioritize which *analyses* should be conducted, compounds that are, or are likely to be, detected by the same analytical methodology have been grouped together:

--*Antibiotics:*[1]

- Those antibiotics quantitated by the FSIS Bioassay multiresidue method (MRM) and associated follow-up methodologies[2] [tetracycline, oxytetracycline, chlortetracycline, beta-lactams (penicillins and cephalosporins; not differentiated within this category), gentamicin, spectinomycin/streptomycin (not differentiated), erythromycin, tilmicosin, tylosin, neomycin, flavomycin, bacitracin, hygromycin, novobiocin, lincomycin*, pirlimycin*, clindamycin*, spiramycin*, oleandomycin*] *identification by mass spectrometry; not quantitated
- Amikacin (aminoglycoside)
- Apramycin (aminoglycoside)
- Kanamycin (aminoglycoside)
- Spectinomycin (aminoglycoside)
- Streptomycin (aminoglycoside)
- Ampicillin (beta lactam)

[1] It can be seen that many of the compounds detected by the FSIS Bioassay (see footnote 2) are also listed separately. This was done because, even though these compounds could be detected by the Bioassay, FSIS also wished to consider the merits of implementing individual chemical methodologies (generally High Performance Liquid Chromatography [HPLC]) for their analysis. Compounds were considered for chemical analysis either because: (1) they could be detected by the Bioassay, but not distinguished from other compounds (e.g.., spectinomycin and streptomycin); or (2) they could be detected by the Bioassay, but the chemical method offered a significantly and usefully lower Limit of Quantitation (LOQ) (e.g., tilmicosin). [In this document, LOQ refers to the lowest level at which the residue can be quantitated. A lower LOQ results in more detailed low-level data on residue occurrences. Data on low-level residue occurrences is needed when generating exposure estimates for risk assessment, and is useful in planning future residue programs.]

[2] FSIS quantitates most antibiotics using a 7-plate Bioassay that measures microbial inhibition. The pattern of inhibition (i.e., the combination of plates showing inhibition) is used to identify the antibiotic. There are some antibiotics, however, that share the same pattern of inhibition. In these cases, it is necessary to undertake follow-up testing (High Performance Liquid Chromatography [HPLC] or mass spectrometry) to identify the compound, where such follow-up methodologies are available. The compounds that share patterns of inhibition, and which are individually identified through follow-up testing, are:

tetracycline/oxytetracycline/chlortetracycline - compounds individually identified by follow-up with HPLC method for tetracyclines

tilmicosin/tylosin - differentiated by mass spectrometry

- Amoxicillin (beta lactam)
- Cloxacillin (beta lactam)
- Hetacillin (beta lactam)
- Ticarcillin (beta lactam)
- Ceftiofur (cefalosporin)
- Cefazolin (synthetic cefalosporin)
- Chloramphenicol
- Florfenicol (chloramphenicol derivative)
- Thiamphenicol (chloramphenicol derivative)
- Fluoroquinolones in FSIS MRM (ciprofloxacin, desethyleneciprofloxacin, danofloxacin, difloxacin, enrofloxacin, marbofloxacin, orbifloxacin, and sarafloxacin)
- Avoparcin (glycopeptide)
- Vancomycin (glycopeptide)
- Clindamycin (lincosamide)
- Lincomycin (lincosamide)
- Pirlimycin (lincosamide)
- Oleandomycin (macrolide)
- Spiramycin (macrolide)
- Tilmicosin (macrolide)
- Tylosin (macrolide)
- Colistin (polypeptide antibiotic)
- Virginiamycin

--*Other Veterinary Drugs:*
- Amprolium (coccidiostat)
- Arsenicals (detected as elemental arsenic)
- Avermectins in FSIS MRM (doramectin, ivermectin, and moxidectin) (antiparasitics)
- Eprinomectin (avermectin)
- Benzimidazoles (anthelmintic)
- Berenil (antiprotozoal)
- Beta agonists, unapproved (incl. clenbuterol, cimaterol, fenoterol, mabuterol, salbutamol, brombuterol, and terbutaline) (growth promotants)
- Ractopamine (beta agonist)
- Carbadox (antimicrobial)
- Clorsulon (anthelmintic)
- Dexamethasone (glucocorticoid)
- Methyl prednisone (glucocorticoid)
- Prednisone (glucocorticoid)
- Halofuginone (antiprotozoal, coccidiostat)
- Hormones, naturally-occurring (17-β estradiol, progesterone, testosterone)
- DES (hormone, synthetic) (estrogenic)
- MGA (hormone, synthetic) (estrus regulator)
- Trenbolone (hormone, synthetic) (anabolic)
- Zeranol (hormone, synthetic) (anabolic)
- Lasalocid (coccidiostat)
- Levamisole (anthelmintic)
- Morantel and pyrantel (anthelmintic)
- Nicarbazin (coccidiostat)

- Nitrofurans (incl. furazolidone, nitrofurazone) (antimicrobial)
- Nitromidazoles in FSIS MRM (dimetridazole, ipronidazole) (antiprotozoals)
- Ronidazole (nitroimidazole) (antimicrobial)
- Etodolac (non-steroidal anti-inflammatory drug [NSAID])
- Flunixin (NSAID)
- Phenylbutazone (NSAID)
- Dipyrone (NSAID)
- Sulfonamides in FSIS MRM (incl. sulfapyridine, sulfadiazine, sulfathiazole, sulfamerazine, sulfamethazine, sulfachloropyridazine, sulfadoxine, sulfamethoxypyridazine, sulfaquinoxaline, sulfadimethoxine, sulfisoxazole, sulfacetamide, sulfamethoxazole, sulfamethizole, sulfanilamide, sulfaguanidine, sulfabromomethazine, sulfasalazine, sulfaethoxypyridazine, sulfaphenazole, and sulfatroxazole) (antibacterials, some are coccidiostats or anitmicrobials)
- Sulfanitran (antibacterial, coccidiostat)
- Thyreostats (incl. thiouracil)
- Veterinary tranquilizers in FSIS MRM (azaperone and its metabolite azaperol, xylazine, haloperidol, acetopromazine, propionylpromazine, and chlorpromazine)

RANKING OF CANDIDATE COMPOUNDS

COMPOUND SCORING

Using a simple 4-point scale (4 = high; 3 = moderate; 2 = low; 1 = none), the SAT scored each of the above veterinary drugs or drug classes in each of the following categories:

- FSIS Historical Testing Information on Violations
- Regulatory Concern
- Lack of FSIS Testing Information on Violations
- Withdrawal Time
- Impact on New and Existing Human Disease
- Relative Number of Animals Treated
- Acute or Chronic Toxicity Concerns

Definitions of each of these categories, and the criteria used for scoring, appear at the end of this section is the "*Scoring Key for Veterinary Drugs, 2000 Domestic Residue Program*."

The results of the compound scoring process are presented in Table 4.1, *Scoring Table for Veterinary Drugs*.

COMPOUND RANKING

Background

As stated above, FSIS chose to employ techniques and principles from the field of risk assessment to obtain a ranking of the relative public health concern represented by each of the above candidate compounds or compound classes.

If FSIS were in possession of detailed historical data on the distribution of levels of each of the candidate compounds or compound classes in meat, poultry, and egg products, then that information could be

combined with consumption data to estimate exposure. By combining these exposure data with toxicity information, risk estimates for each compound or compound class could be generated:

Risk = Exposure x Toxicity (4.1)
= Consumption x Residue Levels x Toxicity
= Consumption x "Risk Per Unit of Consumption"

Given the limited resources available for this priority-setting effort, FSIS did not attempt to associate different degrees of risk with different degrees of exceedance of the tolerance or action level. FSIS instead determined that the best available method for the measurement of relative toxicity is associated with the tolerance or action level. *Specifically, the frequency of violation of the tolerance or action level was used as an indicator of the risk per unit of consumption of a product.*

The first criterion evaluated in Table 4.1, "FSIS Historical Testing Information on Violations," is based on the percent of tested carcasses found to have residues in excess of the tolerance or action level. Specifically, compounds were scored by two methods: (a) the maximum violation rate seen in any production class (averaged over 1989 - 1998); and (b) the maximum, for any class, of the violation rate (again, averaged over 1989 - 1998), but weighted by the size of the production class. The final score for each drug was assigned based on the highest of these two scores.[3] Therefore, it can be seen from Equation (4.1) that the violation rate scores assigned in Table 4.1 represent a rough overall estimate of *relative* risk per unit of consumption.[4] However, for the many candidate compounds or compound classes of concern that have never been included in the FSIS NRP, data on violation rates is not available. It was therefore necessary to generate an estimate of the overall violation rate for each these untested compounds and compound classes.

Estimating the Violation Rate

"Regulatory Concern," "Withdrawal Time," and "Relative Number of Animals Treated" were chosen as scoring categories because it was expected that each of these would be positively correlated with the violation rate. Therefore, they might serve as predictors of violations in those compounds or compound classes for which no reliable historical testing information was available. As indicated in the *Scoring Key for Veterinary Drugs*, the "Regulatory Concern" category was designed to predict the "likelihood of occurrence of violations, based on regulatory intelligence information about possible misuse." "Withdrawal Time" is expected to correlate with "FSIS Historical Testing Information on Violations" because a longer withdrawal time is less likely to be properly observed. When the withdrawal time is not observed prior to slaughter, the carcass may contain violative levels of residues, since the time necessary for sufficient metabolism and/or elimination of the drug would not have passed. "Relative Number of Animals Treated" is expected to correlate with "FSIS Historical Testing Information on Violations" simply because heavy compound use increases the likelihood of violations.

Recall that violation rate data are available for selected compounds and compound classes. Using the scores assigned to these compounds and compound classes, it was possible to evaluate how well the above criteria were correlated. In an effort to impute values for the missing data, a linear regression

[3] For a more detailed explanation, refer the *Scoring Key for Veterinary Drugs.*

[4] While some consideration was given to the size of the production class in scoring "FSIS Historical Testing Information on Violations," no systematic weighting was applied to the scores in this category based upon consumption. Hence the scores assigned to this category represent relative risk *per unit of consumption*, rather than relative risk. To obtain values for relative risk, the scores in this category must be multiplied by the consumption data for each individual production class. This calculation is implemented subsequently, in Phase IV, Equation (4.6).

model was applied. The dependent variable in this model was the category “FSIS Historical Testing Information on Violations," while the only significant independent variable was the product of the “Regulatory Concern” and “Relative Number of Animals Treated.”

Table 4.1 lists 10 compounds or compound classes for which current, reliable data were available to score the category "FSIS Historical Testing Information on Violations," and 52 compounds or compound classes for which they were not. A least squares linear regression model, using the independent variable from the 10 scored compounds or compound classes, was used to predict scores in the category "FSIS Historical Testing Information on Violations" for remaining 52. The following equation was derived:

$$Vp = 0.20(R*N) + 0.73 \qquad (4.2)$$

where Vp= Predicted score for "FSIS Historical Testing Information on Violations"
R = score for "Regulatory Concern"
N = score for "Relative Number of Animals Treated"
R*N = product of R and N.

This model is the result of using a stepwise regression with several possible independent variables. The independent variables available for the stepwise regression were:

1. A score for Regulatory Concern (R)
2. A score for Withdrawal Time (W)
3. A score for Relative Number of Animals Treated (N)
4. R^2
5. W^2
6. N^2
7. The product of R and W
8. The product of R and N
9. The product of W and N.

No terms involving the withdrawal time were included in the final equation since none were found to be significant factors in the regression model.

The model represented by Equation (4.2) was significant, with an overall model p-value of 0.0001, and an R^2 value of 0.93, accounting for 93 percent of the variability in the data.

Where current, reliable historical testing data were available for a compound or compound class, FSIS used the score assigned in Table 4.1. Where current, reliable historical data were not available, FSIS used the predicted score generated by Equation (4.2).

Rating the Veterinary Drugs According to Relative Public Health Concern

As indicated above, the score for "FSIS Historical Testing Information on Violations," combines information on residue levels and toxicity, and thus represents a rough overall estimate of the relative risk per unit of consumption for each drug or drug class. Although this score, once multiplied by relative consumption data for each production class, would conform most closely to a purely risk-based ranking, FSIS believes that additional attributes should also be considered in the ranking. Thus, the ranking according to relative public health concern incorporates, as modifiers, the remaining scoring categories presented in Table 4.1:

Relative Public Health Concern = *Predicted* or *Actual* score for (4.3)
"FSIS Historical Testing Information on Violations" (Estimate of Relative Hazard)
x *modifier for* "Acute or Chronic Toxicity Concerns"
x *modifier for* "Impact on New and Existing Human Disease"
x *modifier for* "Lack of FSIS Testing Information on Violations"

The finding of a violation means that a compound was found at a level where the likelihood of a toxic effect exceeds the Food and Drug Administration's (FDA's) standards (typically 1 in 1,000,000). However, this does not address the *severity* of the effect associated with the toxic endpoint. To capture this concern FSIS has added a modifier for "Acute or Chronic Toxicity Concerns." Thus compounds whose toxic effect can be severe (such as chloramphenicol, exposure to which has been associated with aplastic anemia) are given a maximum score in this category.

A modifier has also been added for "Impact on New and Existing Human Disease." This represents the extent to which the use or misuse of this compound will contribute to new and existing human disease. For example, there is a possibility that the creation of antibiotic-resistant human pathogens may result from the use of antibiotics in animals. This represents a potential public health concern that is not captured by the violation rate.

Finally, the modifier for "Lack of FSIS Testing Information on Violations" has been incorporated because sparse or dated data, or a complete lack of data altogether, increase the relative public health need to obtain information on residue violations for a compound or compound class. In other words, consider two hypothetical compounds, A and B. Suppose FSIS has sampled extensively for compound A, and that A's violation rate earns it a score of "3" in that category. Further suppose that FSIS has never sampled for compound B but that, based on its scores in the “Regulatory Concern,” “Withdrawal Time,” and “Number of animals treated” categories, B has a *predicted* violation rate score of "3." Also assume that A and B have been assigned identical scores in all other categories. FSIS believes there is greater relative need to sample for B than for A, because FSIS has extensive information on A, but none on B.

The use of modifiers presents an element of arbitrariness, as there are no fundamentally "correct" assumptions for the appropriate weight that should be given to each. The approach of FSIS was to consider several alternative sets of weighting factors, and assess the robustness of the final ranking. In Table 4.2, *Veterinary Drug Residues Rated with Various Weighting Formulas*, the drugs are rated for relative public health concern by combining the scoring categories presented in Equation (4.3), above, using four different weighting formulas. In all of the formulas, the score for "FSIS Historical Testing Information on Violations" has been multiplied by a weighted average of the modifiers for "Acute or Chronic Toxicity Concerns" and "Impact on New and Existing Human Disease." These last two categories were combined because they both represent the negative potential public health effects associated with the use of a compound or compound class. The product of these three categories was then multiplied by a modifier for "Lack of FSIS Testing Information on Violations." The formulas differ in the relative weights given to "Acute or Chronic Toxicity Concerns" versus "Impact on New and Existing

Human Disease," and in the magnitude of the modifier for "Lack of FSIS Testing Information on Violations." FSIS chose to use the second of these formulas (bolded and italicized in Table 4.3), based on a consensus about the relative importance of each modifier, and of how much each modifier should be allowed to alter the underlying risk-based score, "V," in Equation (4.4), below. FSIS tested a variety of mathematical formulas to help guide this judgmental process. The value of the selected mathematical formula is that it formalizes the basis of FSIS's judgement. This enables others to observe and understand the adjustments that were made, and it ensures consistency in how these adjustments were applied across a wide range of compounds. Equation (4.4) summarizes the way final adjustments were made.

Relative public health concern rating, veterinary drugs (4.4)
$= V*((D+3*T)/4) *\{1+[(L-1)*0.05]\}$

Where: V = *Predicted* or *Actual* score for "FSIS Historical Testing Information on Violations "
D = score for "Impact on New and Existing Human Disease"
T = score for "Acute or Chronic Toxicity Concerns"
L = score for "Lack of FSIS Testing Information on Violations

In this formula, the category of "Acute or Chronic Toxicity Concerns" was given three times the weight of "Impact on New and Existing Human Disease," because the former represents known direct health effects, while the latter represents possible indirect health effects. In addition, in this formula, the final ratings of compounds or compound classes receiving scores of 4, 3, 2, and 1 in "Lack of FSIS Testing Information on Violations" would be increased by 15%, 10%, 5%, and 0% respectively. In other words, the rating of a compound or compound class that had never been tested by FSIS (in the production classes and matrices of concern) would be increased by 15%, while the rating of one that had been recently tested by FSIS (again, in the production classes and matrices of concern) would remain unchanged.

All of the formulas used here for the veterinary drugs, and below for the pesticides, have been normalized. For a given drug or drug class, this permits comparison of the scores generated by the four different weighting formulas presented in Table 4.2. Because the formulas for the pesticides use different terms (i.e., scoring categories) from those for the veterinary drugs, their scores are not precisely comparable. However, as a result of the normalization the scores for the pesticides and veterinary drugs are comparable in magnitude, thus enabling at least a rough comparison to be made across these two very different categories of compounds.

In Table 4.3, *Veterinary Drug Residues Rated with Various Weighting Formulas, Sorted by Rating*, the drugs are ranked by their rating scores, as generated using each of the four different weighting formulas (again, the results obtained with the selected formula are bolded and italicized). Inspection of this chart reveals the extent to which changes in the weighting formula result in changes in ranking. In this case, the results from the four formulas are similar. The scores presented in Table 4.3 enable FSIS to bring consistency, grounded in formal risk-based considerations, to its efforts to differentiate among a very diverse range of drugs and drug classes in a situation that is marked by minimal data on relative exposures**.** These rankings do not account for differences in exposure due to differences in overall consumption.[5] Data on relative consumption are applied subsequently, in Phase IV, when relative exposure values for each compound/production class (C/PC) pair are estimated.

A key to the abbreviations used in Table 4.3 is presented in Table 4.4, *Key to Abbreviations Used for Veterinary Drugs*.

[5] See footnote 4.

PHASE II - SELECTING DRUGS FOR INCLUSION IN THE 2000 NRP

Following the completion of the ranking of the veterinary drugs, FSIS (1) used these rankings to select those compounds and compound classes that should be included in the 2000 NRP, based purely on their relative public health concern and (2) determined which of these compounds and compound classes actually could be included in the 2000 NRP, based on the availability of laboratory resources.

The consensus of FSIS and FDA was that those compounds and compound classes ranked 34th or higher (out of a total of 62) represented a potential public health concern sufficient to justify their inclusion in the 2000 NRP. In addition, FDA expressed an interest in having FSIS perform limited testing on one compound that did not fall within this group of 34 (veterinary tranquilizers, ranked 56th, in market hogs). This compound was thus also identified as a candidate for inclusion.

Once the high-priority compounds and compound classes had been identified, it was necessary for FSIS to apply considerations beyond those related to public health to determine the compounds for which the Agency would sample. The principal consideration not related to public health was the availability of laboratory resources, especially the availability of appropriate analytical methods within the FSIS laboratories. Based on these considerations, FSIS plans to include the following veterinary drugs in the 2000 Monitoring Plan and Special Projects:

--*Antibiotics:*

- Those antibiotics quantitated by the FSIS Bioassay multiresidue method (MRM) and associated follow-up methodologies[6] [tetracycline, oxytetracycline, chlortetracycline, beta-lactams (penicillins and cephalosporins; not differentiated within this category), gentamicin, spectinomycin/streptomycin (not differentiated), erythromycin, tilmicosin, tylosin, neomycin, flavomycin, bacitracin, hygromycin, novobiocin, lincomycin*, pirlimycin*, clindamycin*, spiramycin*, oleandomycin*] *identification by mass spectrometry; not quantitated
- Spectinomycin (aminoglycoside)
- Chloramphenicol
- Florfenicol (chloramphenicol derivative)
- Fluoroquinolones in FSIS MRM (ciprofloxacin, desethyleneciprofloxacin, danofloxacin, difloxacin, enrofloxacin, marbofloxacin, orbifloxacin, and sarafloxacin)
- Tilmicosin (macrolide)

--*Other Veterinary Drugs:*

- Arsenicals (detected as elemental arsenic)
- Avermectins in FSIS multiresidue method (MRM) (incl. doramectin, ivermectin, moxidectin) (antiparasitics)
- Beta agonists, unapproved (incl. clenbuterol, cimaterol) (growth promotants)
- Ractopamine (beta agonist)
- Carbadox (antimicrobial)
- Dexamethasone (glucocorticoid)
- DES (hormone, synthetic) (estrogenic)
- MGA (hormone, synthetic) (estrus regulator)
- Zeranol (hormone, synthetic) (anabolic)

[6] See footnote 2.

- Nitromidazoles in FSIS MRM (dimetridazole, ipronidazole) (antiprotozoals)
- Flunixin (NSAID)
- Phenylbutazone (NSAID)
- Sulfonamides in FSIS MRM (incl. sulfapyridine, sulfadiazine, sulfathiazole, sulfamerazine, sulfamethazine, sulfachloropyridazine, sulfadoxine, sulfamethoxypyridazine, sulfaquinoxaline, sulfadimethoxine, sulfisoxazole, sulfacetamide, sulfamethoxazole, sulfamethizole, sulfanilamide, sulfaguanidine, sulfabromomethazine, sulfasalazine, sulfaethoxypyridazine, sulfaphenazole, and sulfatroxazole) (antibacterials, some are coccidiostats or anitmicrobials)
- Veterinary tranquilizers in FSIS MRM (azaperone and its metabolite azaperol, xylazine, haloperidol, acetopromazine, propionylpromazine, and chlorpromazine)

Thus, in the 2000 NRP, FSIS plans to employ 19 methodologies that analyze for veterinary drugs (DES and zeranol are detected by a single method). Ten are single-compound methodologies, and nine are MRM's (phenylbutazone is detected by the FSIS multi-residue method for chlorinated hydrocarbon and chlorinated organophosphate compounds). Together, these methodologies encompass approximately over 70 different compounds (groups of individual drugs that are not differentiated have been counted as only a single compound). Note that sampling plans for spectinomycin, DES, and zeranol are tentative, as FSIS is currently attempting to obtain suitable methodologies for these compounds.

Table 4.5, *Rank and Status for Veterinary Drugs*, lists all of the original candidate veterinary drugs in rank order. This table specifies whether each compound or compound class will be sampled under the 2000 Monitoring Plan or Special Projects, or will not be included in the 2000 NRP. For each highly ranked compound or compound class that was not included in the 2000 NRP, a brief explanation of the reason for its exclusion is provided. This table will be used to identify future method development needs for veterinary drugs for the FSIS NRP.

PHASE III - IDENTIFYING THE COMPOUND/PRODUCTION CLASS (C/PC) PAIRS

The SAT participants (principally those from FDA) identified the production classes of concern for each of the drugs and drug classes to be included in the 2000 NRP. These determinations were based upon professional judgment of the likelihood of finding violations within each production class (information examined included use approvals, extent of use, evidence of misuse and, if available, past violation history), combined with the proportion of total domestic meat consumption each production class represented. The results are presented in Table 4.6, *Production Classes Considered for Each Veterinary Drug/Drug Class*. C/PC pairs included in the 2000 NRP are designated by a "●." Those C/PC pairs that are of regulatory concern, but that could not be included in the 2000 NRP because of laboratory resource constraints, are marked with a "○." Since all production classes will be sampled by the chlorinated hydrocarbon/chlorinated organophosphate (CHC/COP) method (see Section 6), and since this method also detects phenylbutazone, the latter will, by default, likewise be sampled in all production classes. However, phenylbutazone is not of regulatory concern in all production classes. Those production classes in which phenylbutazone will be sampled, but where it is *not* of regulatory concern, are designated by a "❍" (i.e., these production classes will be sampled for phenylbutazone, but only because it is automatically detected through the CHC/COP methodology).

PHASE IV - ALLOCATION OF SAMPLING RESOURCES

"FULL-RESOURCE" SAMPLING

Table 4.6 lists the estimated domestic consumption of each production class as a percentage of the total consumption of all the production classes in the table. To obtain these estimates, production data were employed as a surrogate for consumption. Specifically, as shown in Equation (4.5), the estimated relative percent of domestic consumption represented by each production class was obtained by dividing the estimated total annual U.S. domestic production (pounds dressed weight) for that class by the total poundage for all production classes listed in Table 6:

$$(\text{Est. rel. \% domestic consumption})_{PC} = \frac{(\text{Annual production, pounds dressed wt.})_{PC}}{\text{Total annual production, all production classes}} \quad (4.5)$$

FSIS has sufficient analytical capability to consider sampling all production classes of concern for the following compound classes: antibiotics (by Bioassay); arsenicals; avermectins; sulfonamides; and phenylbutazone (via the CHC/COP methodology). To establish a relative sampling priority for each C/PC pair, the ranking score for each compound class (as calculated in Table 4.2) was multiplied by the estimated relative percent of domestic consumption for each production class (as calculated using Equation (4.5), and as presented in Table 4.6). This is shown in Equation (4.6):

$$(\text{Relative sampling priority})_{C/PC} = (\text{Ranking score})_{C} \times (\text{Rel. \% domestic consumption})_{PC} \quad (4.6)$$

Equation (4.6) is analogous to the equation used to estimate risk (Equation (4.1)), in which risk per unit of consumption is multiplied by consumption. While the results of Equation (4.6) do not constitute an estimate of risk, they provide a numerical representation of the relative public health concern represented by each C/PC pair, and thus can be used to prioritize FSIS analytical sampling resources according to the latter. Note that the risk ranking provided by Equation (4.6) is based upon average consumption across the entire U.S. population, rather than upon maximally exposed individuals.

In Table 4.7, *Veterinary Drug Compound/Production Class Pairs, Sorted by Sampling Priority Score, "Full Resource" Sampling*, the calculation shown in Equation (4.6) has been carried out for the antibiotics, arsenicals, avermectins, and sulfonamides, for each production class in which the specified drug might appear (as indicated in Table 4.6). The C/PC pairs were sorted by their sampling priority scores, and roughly divided into quartiles. Initially, C/PC pairs in the first though fourth quartile were assigned sampling numbers of 460, 300, 230, and 90, respectively. These priority scores were combined with historical violation rate information for each individual C/PC pair, and information on laboratory sampling capacity to select, for each pairing, from among four different sampling options: very high regulatory concern (460 analyses/year); high regulatory concern (300 analyses/year); moderate regulatory concern (230 samples/year); low regulatory concern (90 samples/year).[7] For antibiotics, because of available laboratory capacity, it was possible to increase sampling of those production classes having the highest regulatory concern to 690 analyses/year. These sampling levels provide varying probabilities of detecting residue violations. Thus the larger sample sizes, which provide the greater chance of detecting violations, are directed towards those C/PC pairs that have been identified as representing higher levels of relative public health concern. Statistically, if the true violation rate is 1%, the probabilities of detecting at least one violation with sampling levels of 690, 460, 300, 230, and 90 are 99.9%, 99%, 95%, 90%, and 60% (85% at a 2% violation rate), respectively.

[7]For reasons explained below, arsenicals in young chickens were scheduled to be sampled at a still higher level of 1200/analyses per year.

ADJUSTING RELATIVE SAMPLING NUMBERS

Adjusting for historical data on violation rates of individual C/PC pairs

As described above, FSIS used "FSIS Historical Testing Information on Violations" as a critical factor in ranking the various drugs and drug classes according to their relative public health concern. Because this information is available for each production class individually, it can also be used to further refine the relative priority of sampling each C/PC pair. Table 4.8, *Adjusted Number of Analyses for Each Veterinary Drug Compound/Production Class Pair, "Full Resource" Sampling*, lists the number of analyses assigned to each C/PC pair in Table 4.7. It also lists, for the period 1/1/89 - 12/31/98, the total number of samples analyzed by FSIS under its Monitoring Plan and Special Projects (i.e., random sampling only) for each C/PC pair, and the percent of samples found to be violative (i.e., present at a level in excess of the action level or regulatory tolerance; or, for those compounds that are prohibited, present at any detectable level). Using this data, the following rules were applied to adjust the sampling numbers:

1. C/PC pair never tested: +1 level (i.e., increase by one sampling level, e.g., from 230 samples to 300 samples)
2. At least 300 samples tested, violation rate $\geq$ 0.50%, but < 0.70%: +1 level
3. At least 300 samples tested, violation rate $\geq$ 0.70%: +2 levels
4. At least 300 samples tested, violation rate = 0.00%: -1 level
5. The maximum number of samples to be scheduled for testing is 460.

The two exceptions to this are:

1. Geese are never to be scheduled for more than 90 samples. Because very few geese are produced, and because virtually all geese are slaughtered by a very limited number of plants, it is impractical to collect a larger number of samples.
2. Sampling for antibiotics was permitted to rise to a fifth sampling level, of 690 analyses/year.

All of the above adjustments were applied, and the sampling numbers obtained following these adjustments are listed in Table 4.8 under the heading "INITIAL ADJ. #" (initial adjusted number of samples).

Adjusting for laboratory capacity

Following this, it was necessary to make a final set of adjustments to match the total sampling numbers for each compound class with the analytical capabilities of the FSIS laboratories. No adjustments were necessary for the avermectins or sulfonamides, since there was a close correspondence between the proposed number of samples listed in Table 4.8 and FSIS laboratory capacity.

For the antibiotics, FSIS laboratory capacity slightly exceeded the proposed number of samples. FSIS decided to use this excess capacity to improve the quality of information collected, by setting a 230-sample minimum for all production classes (except geese, as explained above). This additional laboratory capacity also explains why sampling for antibiotics was not restricted to a maximum of 460 samples per C/PC pair.

For the arsenicals, a judgement was made to increase the number of analyses in young chickens from 460 to 1200. The basis for this decision was that: (a) arsenical violations have averaged a relatively significant 0.41% between 1989 - 1998; (b) young chickens are the largest production class (constituting an estimated 41%, by weight, of total domestic consumption of meat, poultry and egg products), and

violations in young chickens thus represent a relatively larger public exposure than violations in smaller production classes; and (c) laboratory capacity for this increased sampling was available.

The sample numbers obtained following all needed adjustments for laboratory capacity are listed in the last column of Table 4.8, under the heading "FINAL ADJ. #" (final adjusted number of samples).

"LIMITED RESOURCE" SAMPLING

The 2000 NRP includes a number of compounds never before sampled by FSIS. In sampling these compounds, FSIS was most concerned with obtaining information on their occurrence in particular production classes where it was suspected they might be of concern. To enable FSIS to sample this entire range of compounds, it was necessary to limit the number of samples taken per compound. In apportioning this "limited resource" sampling among the production classes of concern, it was particularly important to ensure that a sufficient number of samples was taken from each production class analyzed. If too few samples were taken from a production class, and no violations were detected, it would be difficult to interpret such a result (the interpretation could not be informed by data from earlier sampling, because no such sampling exists). With a small number of samples, the lack of a detected violation might mean that the true violation rate was very low, or it might mean that the true violation rate was high but that too few samples were taken to detect a violation. Thus, as a general policy for all domestic sampling of new compounds, a minimum of 300 analyses was to be carried out in each production class sampled. This yields a 95% chance of detecting a violation, if the true violation rate were 1%.

For example, FSIS has the capacity to conduct 300 florfenicol analyses in 2000, and two production classes were identified as being of concern for this compound. Thus FSIS could carry out either 300 analyses in one of the production classes, or 150 analyses in each. However, since FSIS has not analyzed for florfenicol previously, and will analyze a minimum of 300 samples per production class for new compounds, the Agency can only analyze one production class for florfenicol. Thus FSIS chose to conduct domestic florfenicol sampling in the highest priority of the two production classes, which FDA designated as dairy cows.

Selection of production classes for the remainder of the limited resource compounds was made as follows:

Beta agonists are of concern in steers, formula-fed veal, and market hogs. The analytical capacity for beta agonists in 2000 is 900 samples. FSIS will work with FDA to conduct 300 analyses for beta agonists in each of these three production classes.

Carbadox is of concern in market hogs, roaster pigs, boars/stags, and sows. The analytical capacity for domestic sampling of carbadox in 2000 is 300 samples, and the top priority production class is roaster pigs. Thus FSIS will conduct 300 analyses for carbadox in roaster pigs.

DES is of concern in heifers, steers, and formula-fed veal, and zeranol is of concern in formula-fed veal and non-formula-fed veal. The top priority production class for both of these compounds is formula-fed veal. The number of analyses for DES and zeranol has not yet been determined, as sampling for these compounds is contingent upon improving the sensitivity of the current methodology to approximately 10 parts per trillion (ppt). FSIS will undertake sampling when this improved senstivity is achieved.

Dexamethasone is of concern in eight different production classes. The analytical capacity for domestic sampling of dexamethasone in 2000 is 300 analyses, and the top priority production class is dairy cows. Thus FSIS will conduct 300 analyses for dexamethasone in dairy cows.

Florfenicol is of concern in dairy cows and heavy calves. The analytical capacity florfenicol in 2000 is 300 analyses, and the top priority production class dairy cows. Thus, FSIS will conduct 300 analyses for florfenicol in dairy cows.

Flunixin is of concern in dairy cows, and the analytical capacity for domestic sampling of flunixin in 2000 is 300 analyses. FSIS will therefore conduct 300 analyses for flunixin in dairy cows.

Fluoroquinolones are of concern in seven different production classes. The analytical capacity for domestic sampling of fluoroquinolones in 2000 is 900 analyses, and the top three priority production classes are dairy cows, market hogs, and young chickens. FSIS will conduct 300 analyses for fluoroquinolones in each of these three production classes.

MGA is of concern in heifers, steers, formula-fed veal, and non-formula fed veal.. The analytical capacity for MGA in 2000 is 500 samples, and the top priority production classes are heifers and steers. FSIS will thus conduct 250 analyses for MGA in each of these two production classes.

Nitroimidazoles are of concern in formula-fed veal and market hogs. The analytical capacity for domestic sampling of nitroimidazoles in 2000 is 260 samples, and the top priority production class is formula-fed veal. Thus, FSIS will conduct 260 analyses for nitroimidazoles in formula-fed veal.

Ractopamine is of concern in market hogs and roaster pigs. The analytical capacity for domestic sampling of ractopamine in 2000 is 300 samples, and the top priority production class is market hogs. FSIS will conduct 300 analyses for ractopamine in market hogs.

Spectinomycin is of concern in dairy cows. Thus, FSIS plans to sample for spectinomycin in dairy cows. However, the number of analyses for spectinomycin has not yet been determined, as sampling is contingent upon successful optimization of the instrument needed to perform the analysis.

Tilmicosin is of concern in seven different production classes. The analytical capacity for tilmicosin in 2000 is 840 samples, and the top priority production classes are dairy cattle, beef cattle, and steers. FSIS will conduct 300 analyses for tilmicosin in each of dairy cattle and beef cattle, and 240 analyses in steers.

Veterinary tranquilizers are of concern in market hogs and dairy cows. The analytical capacity of veterinary tranquilizers in 2000 is 300 samples, and the top priority production class is market hogs. FSIS will therefore conduct 300 screening tests for veterinary tranquilizers in market hogs.

The above information is presented in tabular format at the end of Section 9 in Table 9.1, *Sampling Plan for All Veterinary Drug and Pesticide Compound/Production Class Pairs*, and in Table 9.3, *Summary, 2000 FSIS National Residue Program, Domestic Monitoring Plan and Special Projects and Import Residue Plan*.

NOTE ON SEASONALITY

Many of the residues sampled under the limited-resource category will be analyzed over a period of three to four months, rather than over an entire year. This was done because, to cover such a wide range of residues, it was necessary for FSIS to maximize laboratory efficiency. It is more efficient to dedicate instrumentation and analysts to a small number of compounds, finish those analyses, and then change to a

new set of analyses, rather than attempting to maintain analytical capacity for all of the above analytes simultaneously.

For those compounds where sampling was limited to a few months, and where usage was judged to be seasonal, sampling was scheduled to coincide with the period of greatest suspected usage.

SCORING KEY FOR VETERINARY DRUGS
2000 FSIS DOMESTIC RESIDUE PROGRAM

FSIS Historical Testing Information on Violations (1/1/89 - 12/31/98)

Violation rate scores were calculated by two different methods, A and B:

Method A: Maximum Violation Rate. Identify the production class exhibiting the highest average violation rate (the number of violations over the period from 1989 - 1998, divided by the total number of samples analyzed). Score as follows:

4 = > 1.0%
3 = 0.50% - 1.0 %
2 = 0.15% - 0.49%
1 = < 0.15%
NT = Not tested by FSIS
NA = Tested by FSIS, but violation information does not apply

Method B: Violation Rate Weighted by Size of Production Class. For each production class analyzed, multiply the average violation rate (defined above) by the relative consumption value for that class (weight annual U.S. production for that class, divided by total production for all classes for which FSIS has regulatory responsibility). Add together the values for all production classes. Score as follows:

4 = > 0.15%
3 = 0.076% - 0.15%
2 = 0.01% - 0.075%
1 = < 0.01%
NT = Not tested by FSIS
NA = Tested by FSIS, but violation information does not apply

Final score is determined by assigning, to each drug or drug class, the greater of the scores from Method A and Method B.

It can be seen that Method A identifies those drugs that are of regulatory concern because they exhibit high violation rates, independent of the relative consumption value of the production class in which the violations have occurred. Method B identifies those drugs that may not have the highest violation rates, but would nevertheless be of concern because they exhibit moderate violation rates in a relatively large proportion of the U.S. meat supply. By employing Methods A and B together, and assigning a final score based on the highest score received from each, both of the above concerns are captured.

Regulatory Concern

This consists of professional judgments made about the likelihood of occurrence of violations, based on regulatory intelligence information about possible misuse. Due to the public health significance of drug residue violations, surveillance data pertaining to a compound must meet only one of the requirements listed under each number below to receive that numerical ranking.

4 = Well-documented intelligence information gathered from a variety of reliable sources indicates possible widespread misuse of the compound, and/or this compound is banned, or is on the list of

compounds prohibited from use in food animals under AMDUCA, or is not approved for use in the U.S.

3 = Intelligence information gathered through a variety of sources indicates only occasional misuse of this compound. The dosage form/packaging of this compound has potential for misuse.

2 = Intelligence information rarely indicates misuse of this compound.

1 = Intelligence information has never indicated misuse of this compound.

Lack of FSIS Testing Information on Violations

This represents the extent to which FSIS analytical testing information on a residue is limited, absent or obsolete.

4 = FSIS has not included this compound in its sampling program within the past 10 years (1/1/89 - 12/31/98); or FSIS has included this compound within its program only between 6 and 10 years ago (1/1/89 - 12/31/93), but the sampling does not meet the criteria specified for a "3;" or FSIS has included this compound in its sampling program, but the information is not at all useful in predicting future violation rates, because of subsequent significant changes in the conditions of use of the compound (e.g., the reduction in withdrawal time for carbadox), or because regulatory intelligence information indicates that the situation has changed significantly since the last time the compound was sampled; or because the compound is of concern in several production classes of interest, but testing has been carried out in only one.

3 = FSIS has tested within the past 5 years (1/1/94 - 12/31/98), but in fewer than 75% of the production classes of interest; or the only testing was between 6 and 10 years ago, where FSIS has analyzed at least 75% of production classes of interest for at least 2 of these 5 years, with a total of at least 500 samples per production class during this 5-year period and, in the case of a multi-residue method, the method used covers all compounds of interest with the compound class; or, the compound would normally have qualified for a "1" or "2," but the method used was not sufficiently sensitive to permit accurate determination of the true violation rate.

2 = FSIS has included this compound in its sampling program within the past 5 years in at least 75%, but less than 100% of the production classes of interest; or 100% of the production classes of interest have been sampled, but the amount and duration of sampling has been insufficient to qualify for a "1."

1 = FSIS has included this compound in its sampling program within the past 5 years, and has analyzed each production class of interest for at least 2 of these 5 years, with a total of at least 500 samples per production class during this 5-year period, and in the case of a multi-residue method, the method used covers all compounds of interest with the compound class.

Withdrawal Time

Producers using approved animal drugs are required to follow approved "conditions of use." For each drug, in each production class in which it is approved, the conditions of use specify the dosing regimen and the withdrawal time. The withdrawal time is the number of days that must pass between completion of the dosing regimen and the time of slaughter. This allows sufficient time for the concentration of drug in the animal to decrease below the tolerance. For approved drugs, the following scores were used. For unapproved drugs, scores in this category were assigned based on estimates of their half-lives.

4 = Withdrawal time greater than 14 days

3 = Withdrawal time between 8 and 14 days

2 = Withdrawal time between 1 and 7 days

1 = Zero-day withdrawal time

Impact on New and Existing Human Disease

This represents the extent to which the use or misuse of this compound may contribute to new and existing human disease. Examples could include the possible creation of antibiotic-resistant human pathogens from the use of antibiotics in animals, or the potentiation of new zoonotic diseases (which might subsequently be altered and transferred to humans) following pesticide-induced immunosuppression.

4= Scientific information gathered from a variety of reliable sources indicate that possible widespread use of this compound might significantly modify drug resistance patterns of human pathogenic organisms.

3 = Limited scientific information is available to suggest or document public health risk but compound has the potential to affect microflora.

2 = No scientific information available to suggest or document public health risk.

1 = Current scientific information available suggests no public health risk.

Relative Number of Animals Treated

These scores are based on surveys of treatment practices in animal populations that are representative of national feedlot, dairy, and swine production.

4 = Products containing this drug fall within the top third of those administered to animals treated within a particular category and dosage form of active ingredient.

3 = Products containing this drug fall within the middle third of those administered to animals treated within a particular category and dosage form of active ingredient.

2 = Products containing this drug fall within the bottom third of those administered to animals treated within a particular category and dosage form of active ingredient (but have more usage than products given a score of "1," as defined below).

1 = Products containing this drug are estimated to have extremely limited usage. This category includes all drugs banned under AMDUCA.

Note: Where data were unavailable, scores were estimated, based on comparison to related drugs with known usage levels. Numbers estimated in this way are contained within parentheses.

Acute or Chronic Toxicity Concerns

This represents a combination of the toxicity of the compound and the severity associated with the compound's toxic endpoint

4 = Compound is a carcinogen, or potentially life threatening , or has significant acute effects including the anaphylactic response to an allergen.

3 = Systemic no observed effect levels (NOEL's) seen at intermediate to low doses in laboratory test animals. Antimicrobial effects with a high potential to alter intestinal microflora.

2 = Systemic NOEL's seen at high oral doses in laboratory test animals. Antimicrobial effects with a moderate potential to alter intestinal microflora.

1 = Compound generally shows no toxicity in laboratory test animals even at doses much higher than present in edible tissues at zero-day withdrawal.